UNIVERSITY OF CAPE TOWN

# Factors associated with Nevirapine adherence in the prevention of mother-to-child transmission of HIV in the Free State province of South Africa and discrepancies between service records and cord-blood surveillance



By

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Date: 15 August, 2014

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## ABSTRACT

Sub-Saharan Africa holds 90% of the HIV-infected children worldwide and most of them are infected through vertical transmission. The elimination of mother-to-child transmission of HIV in this region can be achieved through complementing prophylaxis regimens with effective service delivery. The latter should involve reaching all those at risk and optimizing adherence through adequate and routine follow-up. A study set out to assess the effectiveness of preventing mother-to-child transmission (PMTCT) programs in four African countries including South Africa using the simple nevirapine-based PMTCT regimen, found that prophylaxis coverage for the PMTCT of HIV was on average poor, at only 50% among HIV-exposed infants during 2007-2008. Incomplete HIV testing in pregnancy accounted for 46% of missed opportunities for PMTCT intervention. In addition, discrepancies were found between data from cord-blood samples, which are the gold standard measure of ingestion of the prophylaxis by mothers and routinely collected data on the provision of prophylaxis at antenatal clinics. Clinic records overestimated adherence to prophylaxis which could mislead decisions about service delivery. Adherence to the simple nevirapine regimen, data and service quality should be investigated in order to identify needs for strengthening the effectiveness of WHO Option B guidelines which are being rolled out in resource-poor settings.

This project set out to assess the extent of clinic-level PMTCT prophylaxis coverage in the resource-limited setting of the Free State province. Adherence to treatment as well as accuracy of clinic records so as to inform better service implementation were measured. A total of 1572 mother-infant pairs were included in a cross-sectional survey carried out in rural antenatal and delivery services from two health districts between 2007 and 2008. HIV testing and nevirapine prophylaxis data were collected by nurses and compared to anonymously linked cord-blood tests which confirmed true HIV status and ingestion of nevirapine. Logistic regression was used to assess variables from the clinic surveillance data: age, gravidity, mode of delivery, timing of HIV testing and number of antenatal visits during pregnancy, as potential predictors of adherence to nevirapine.

The Kappa statistic revealed a disagreement of 10% in HIV test results and 20% in nevirapine intake between clinic records and cord-blood. The clinic records under-estimated maternal HIV prevalence by 9% (22% records versus 31% cord-blood) in mothers aged between 12 and 43 years. Also, cord-blood surveillance revealed that 19.4% of the HIV positive women recorded to have been offered nevirapine during labor, did not actually ingest it. The more frequently a woman sought antenatal care during pregnancy, the more likely she was to ingest nevirapine. Women who had at least 4 antenatal visits were 4.5 times more likely to adhere than women who attended services only once.

Even though this is the simplest regimen for preventing vertical HIV transmission, compliance to the entire antenatal cascade during pregnancy is important in improving adherence to therapy and preventing missed opportunities for intervention. Inaccurate collection of routine clinic data negatively impacts on routinely reported data outcomes. Major improvements need to be undertaken both at the service provider and user levels in order to ensure that the effectiveness of the new Option-B guidelines are optimal in remote settings.

# 1. CHAPTER 1: Study Protocol

## 1.1 ABSTRACT

At least 90% of HIV-infected children live in sub-Saharan Africa.(1) In Africa, an estimated 3% of children under the age of five die due to HIV/AIDS acquired through vertical transmission, and in some African countries this is as high as 28%.(2) Preventing paediatric HIV infection will contribute to eliminating HIV and create an AIDS-free society in the future. The elimination of mother-to-child transmission (MTCT) of HIV in Africa can only be achieved through complimenting prophylactic regimens with effective service delivery. The latter should involve reaching all those at risk and optimizing adherence through adequate and routine follow-up.(3-5) The PMTCT (prevention of mother-to-child transmission of HIV) Effectiveness in Africa: Research and Linkages to care (PEARL) Study set out to assess the effectiveness of PMTCT programs in African countries. It surveyed four African countries (including South Africa) and found that prophylactic coverage for PMTCT services was on average poor, at only 50% among HIV-exposed infants during the 2007-to-2008 period.(6) The South African data were sampled from the Western Cape and Free State provinces. A subsequent detailed assessment of the data from the Western Cape Province revealed that incomplete testing in pregnancy accounted for 46% of missed opportunities for PMTCT intervention.(7) In addition, discrepancies were found between data from cord-blood samples, which are the gold standard measure of ingestion of the prophylaxis by mothers and routinely collected data on the provision of prophylaxis at antenatal clinics.(7) There were differences in 2.8% of HIV test results where clinics recorded HIV-positive outcomes that tested negative in the corresponding cord-blood samples. Also, clinic records overestimated adherence to prophylaxis which could mislead decisions about service delivery. The Western Cape Province is one region with the best access to ARVS at antenatal services in South Africa (8;9) yet these results show that there is poor linkage between the availability of treatment and effective service delivery. Unlike the Western Cape, the rural area of the Free State province is poorly serviced with some patients waiting more than a month to receive treatment(10) and therefore adherence to treatment and the accuracy of data from PMTCT services should be investigated, in order to assess the quality of services

and identify needs in order to complement the effectiveness of the Option B regimen which is currently underway*. This project set out to assess PMTCT coverage at antenatal services in resource-limited settings of the Free State, adherence to treatment as well as accuracy of clinic records so as to inform better service implementation.

### 1.2 BACKGROUND

The current guidelines for PMTCT programmes set out by the WHO in 2010 aim to significantly reduce vertical transmission of HIV mainly in low income settings.(11) Routine PMTCT data collected during the past three years show that the prevalence of paediatric HIV exposure among infants in South Africa is as high as 32%.(9;12) Despite broader coverage of the recommended prophylactic regimens, HIV vertical transmission at 6 weeks postpartum remained at 3.5% in 2010(9) while it had been successfully eliminated in many developed countries.(11) Global targets have been set at eliminating paediatric HIV by 2015 through incorporating PMTCT of HIV programmes into the existing antenatal and mother-infant health services.(11) Use of fixed-dose combination antiretroviral therapy (ART) instead of AZT and single-dose nevirapine in pregnancy irrespective of CD4 count levels or clinical stage of disease is also being widely promoted(13) to reduce the transmission rate to less than 5% by 2015.(14) However, the level of acceptance and adherence to the simpler single dose nevirapine regimen (15) needs to be known in order to have insight on how achievable combination ART initiation will be in pregnant women. Guidelines on the measurement of the effectiveness of PMTCT programmes at the population/national level have recently been suggested by the WHO.(16) These measures assess the level of success and challenges faced by PMTCT programmes and assess the feasibility of using triple therapy to achieve better outcomes.

The PEARL study assessed PMTCT services across four African countries, Cameroon, Cote d'Ivoire, South Africa and Zambia and revealed that coverage of single-dose nevirapine was poor, with only half of the HIV-exposed infants being protected.(6) Lack of early routine HIV testing and repeat testing at 32-36 weeks also contributes to missed opportunities for

**Further to the completion of this mini-thesis protocol (2013), the South African Department of Health announced in July, 2014, the national implementation of Option B+ from January 2015.*

preventing paediatric transmission.(15;17;18) Analyses of local African PMTCT programmes prior to 2010 that used cord-blood tests for both HIV testing and for the presence of nevirapine, have shown that data from routine clinical records were inaccurate and that the assumption that all drugs dispensed to patients were actually ingested was not valid.(7;19;20)

Although the WHO 2010 PMTCT guidelines recommend early testing and initiation of prophylaxis with repeat testing at 32-36 weeks for those who initially test negative(15;17;18), this may not occur if the health system is not functioning optimally.(21) Furthermore, the most recent South African guidelines recommend daily triple therapy for all HIV-positive pregnant women until cessation of breastfeeding (if mother does not need to continue with therapy for her own health), irrespective of clinical stage of disease and CD4 count levels.(22) In both urban and rural settings the uptake of and adherence to single-dose regimen is poor, and the implementation of the recently proposed triple therapy for every HIV-positive woman will be an even greater challenge. The pre-2010 status of the PMTCT services in the Western Cape Province were reported in 2012 (7) and this study will assess the status of less well-resourced settings in the Free State Province. As the guidelines are continually being updated there is urgency for such assessments.

### 1.3 AIMS

The aim of this study will be to assess PMTCT coverage and identify discrepancies in routinely collected data at facilities and data from a cord-blood survey in the Free State Province.

The objectives will be:

(i) To assess coverage for HIV testing and PMTCT prophylaxis at antenatal services

(ii) To assess adherence to nevirapine prophylaxis and identify factors influencing it

(iii) To identify discrepancies between data routinely recorded by service providers on the provision of HIV testing, the test results and coverage of PMTCT prophylaxis and data from cord-blood samples that confirm HIV testing and PMTCT coverage.

## 1.4 METHODS

### *1.4.1 Data summary*

This is a cross-sectional survey of clinic records and cord-blood surveillance data from the Free State Province of South Africa (2007-2008). The data were collected as part of the PEARL study.(6) The data comprises of 1679 women who delivered at one of ten clinics. A total of 107 (6.4%) of these women did not attend antenatal services prior to delivery and will not be included in our analyses.

#### *1.4.1.1 Definitions*

Effectiveness (of a regimen): The degree to which prophylaxis or therapy prevent transmission of HIV from mother to child

Adherence to nevirapine: presence of nevirapine in the cord-blood sample (confirming ingestion) where clinic records indicate that the drug was dispensed to the woman during pregnancy.

Coverage (for HIV testing and treatment): the proportion of pregnant women attending antenatal facilities who are tested for HIV and the proportion of HIV-positive women who are offered therapy/prophylaxis.

### *1.4.2 Variable distributions*

The main outcome variable is adherence to nevirapine. Five potential determinants of adherence to nevirapine will be investigated (Table 1.4.2).

**Table 1.4.2:** List of variables to be assessed as potential determinants of adherence

| **Variable** | **Variable type : unit of measure** |
|---|---|
| Age | Continuous : years |
| Gravidity | Ordinal : current number of children |
| Mode of delivery | Binary : coding for ‘vaginal’ or ‘caesarean’ |
| First HIV test done before or during current pregnancy | Binary : coding for ‘Before’ or ‘During’ |
| Total number of ANC visits | Ordinal : number of ANC visits before delivery |

### *1.4.3 Analyses to be carried out*

Three main analyses will be carried out to achieve the aims for the project.

(1) The HIV testing coverage and level of adherence to prophylaxis.

**(2)** Identification of factors associated with adherence to nevirapine. Variables which will be assessed in a logistic regression approach are listed in Table 1 and include age of the pregnant woman, gravidity and number of ANC visits. Some of these factors, including mode of delivery will be tested for possibility of effect modification and confounding, for example age and gravidity may be strongly correlated.

(3) Differences and agreement between clinic records and cord-blood results will be assessed. The main comparisons will be on HIV test results and ingestion of prophylaxis. The last time-point for HIV test before delivery will be considered where a HIV-negative record coincides with a positive cord-blood result so as to consider the possibility of late sero-conversion.

### *1.4.4 Statistical Tests*

The outcome variable is binary (i.e., the presence or absence of nevirapine in cord-blood) and hence logistic regression will be used in the identification of influential factors. Table 2 gives a list of proposed statistical tests for each of the analyses objectives.

**Table 1.4.4:** Proposed statistical analyses

| **Analysis objective** | **Proposed specific test** |
|---|---|
| 1. Adherence and Coverage | - Proportions |
| 2. Identifying individual variables that influence adherence | - logistic regression for each variable separately |
| 3. Check for co-variable influences such as confounding and interaction to further refine associations and obtain final list of predictor variables for adherence | - logistic regression with stepwise variable addition assessing AIC and likelihood functions of the models |
| 4. Comparison of clinic surveillance records and cord-blood results | - Kappa statistic |

## 1.5 ETHICS

This project is part of a larger study to assess effectiveness of PMTCT programmes across African countries. It was conducted between 2007 and 2009 (see attached ethical approval: REC Ref 038/2007) in APPENDIX A. Women were informed about this study during their antenatal visits at the clinic by study staff and through posters in the waiting rooms. When data were collected from the clinics, they were not linked to any personal identifiers. Study numbers were used instead of folder numbers or names in order to protect participants' privacy and confidentiality. Therefore the participant could not be traced using the records collected for analyses. There were no anticipated risks for patients associated with this study since the drawing of cord-blood occurred after the birth, using the discarded placenta, and analyses were done outside the clinics on the unlinked data. A copy of the clinic surveillance form which was used to collect individual, anonymous data from the clinic records is attached in APPENDIX B. The results of this analysis will benefit the respective region and the country at large in improved implementation of future PMTCT programmes. This will be achieved through informing the Department of Health about our findings. Also, the outcome of the analyses will be published in a peer-reviewed journal for the benefit of other researchers in the field.

## 1.6 BUDGET

This project will be secondary analyses on data previously collected therefore no budget is required.

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# 2. CHAPTER 2: Literature Review

Nearly all HIV infections in children are through vertical transmission either during pregnancy, labour, child birth or breastfeeding. In the absence of prophylaxis, the risk of transmission ranges between 15% and 40% depending on feeding mode [1]. The infant exposure rates to HIV infection are highest in the Sub-Saharan Africa where nearly a third of global adult infections are found as well as the highest under-5 child mortality rates [2,3]. The World Health Organization (WHO) published evidence-based guidelines in 2010 to be adopted by affected countries in order to reduce mother-to-child transmission (MTCT) of HIV worldwide by half before 2015 [4]. However, better progress was easily achievable in developed countries while the low-to-middle income countries struggled [5]. In South Africa, guidelines have been set and are being implemented towards achieving improved PMTCT targets by 2015, such reducing vertical transmission rate to less than 2% among 6 week- old HIV-exposed infants [6].

## 2.1 Global health efforts to reduce MTCT at the time of the new millennium

The WHO first published evidence-based recommendations for use of antiretrovirals (ARVs) in PMTCT in 2000. Although HIV incidence was higher in Africa, treatment was not easily affordable and thus little progress took place in terms of implementing the guidelines. In 2006, revised guidelines were released specifically aimed at resource-limited settings such as most parts of Africa with the aim of achieving free HIV testing, counselling and treatment for all pregnant women by 2010 [7]. In 2010, the integration of PMTCT programs into routine antenatal services was an important recommendation which made access and delivery easier [4]. This was to enable routine testing for HIV and monitoring of CD4 count levels in particular, so as to ensure timely initiation of treatment and prophylaxis among pregnant women. Evidence from numerous follow-up studies has shown that delaying the initiation of treatment or starting treatment when CD4 count levels are decreasing below 350cells/µl favors rapid progression to AIDS and death [8].

### 2.1.1 *WHO guidelines for PMTCT between 2006 and 2013*

In the 2006 WHO guidelines for lowering mother-to-child transmission (MTCT) of HIV in resource-limited settings, a CD4 count less than 200cells/$mm^3$ or clinical disease stage 4 were highlighted as the critical points at which treatment should be initiated [7]. A CD4 count of 350cells/$mm^3$ was considered if the clinical disease was above stage 2 [7]. These guidelines were complex and difficult to implement, given the human and laboratory resources required for frequent monitoring [9]. However, waiting for a CD4 count less than 200 to initiate therapy is risky and may be too late to ensure recovery [10]. Therefore, in 2010, the WHO published revised guidelines aimed to achieve a vertical transmission rate of less than 5% for 35% exposure and below 2% for a 25% exposure in low-to-middle income countries [11]. In an attempt to streamline guidelines and their implementation, the 2010 guidelines recommended 'Option A' regimen for mothers in need of HIV treatment for their own health, i.e., with CD4 count of less than 350cells/$mm^3$, to continue with daily life-long antiretroviral therapy (ART) throughout antepartum and intrapartum phases of pregnancy [4, 11].

Alternatively, when the CD4 count was above 350cells/$mm^3$ PMTCT prophylaxis was recommended comprising of AZT twice daily beginning from first trimester of pregnancy and at the onset of labour, single-dose of nevirapine and the first dose of a 7-day dual therapy (AZT+3TC) (Table 2.1.1) [11]. Option B proposes that women not eligible for maternal life-long ART, should also receive ART from the first trimester, through childbirth until one week after cessation of breastfeeding or a week after delivery if not breastfeeding [11]. The requirement for monitoring disease progression through CD4 count testing in options A and B, however, can be a disadvantage to HIV-positive women who have no ease of access to such services. The shift from one regimen to another also challenges monitoring and adherence in resource-limited settings. Drug resistance may pose a risk to women not on life-long ART, who interrupt therapy between multiple pregnancies. Therefore, most recent guidelines (2013), which will be adopted nationally in South Africa in 2015, suggest a more aggressive but further simplified approach, Option B+, where all HIV positive mothers should take the daily triple therapy regardless of CD4 count levels for the rest of their lives in order to also protect future pregnancies [9,11,12].

**Table 2.1.1:** WHO treatment and prophylaxis options to prevent vertical transmission of HIV during pregnancy and delivery.

| **Regimen Option (WHO year)** | **Treatment (CD4 count ≤ 350cells/mm$^3$** | **Prophylaxis (CD4 count >350cells/mm$^3$)** | **Started in South Africa** |
|---|---|---|---|
| 2006[#] (at lower CD4 count cutoff of ≤200cells/mm$^3$) | Triple therapy: daily, life-long from diagnosis | AZT: twice daily, from trimester2<br>sd-NVP & first dose of 7-day AZT+3TC: at onset of labour | 2008* |
| Option A (2010) | Triple therapy: daily, life-long from diagnosis | AZT: twice daily, from first trimester<br>sd-NVP & first dose of 7-day AZT+3TC: at onset of labour | 2010* |
| Option B (2010) | Triple therapy: daily, life-long from diagnosis | Triple therapy: daily, from first trimester & through delivery | 2013 |
| Option B+ (2012) | Triple therapy: daily, life-long from diagnosis | Triple therapy: daily, life-long from diagnosis | |

Treatment and prophylaxis options adapted from WHO reports 2010,[9,11]. [#]The CD4 cut-off given applies if woman has clinical disease stage 3 otherwise eligible if CD4 count ≤ 200 cells/mm$^3$ or clinical disease is at stage 4[7]. *excludes 3TC from the regimen.

## 2.2 Coverage, uptake and effectiveness of PMTCT regimens in sub-Saharan Africa

In 2008, at least two detailed guidelines had already been published by the WHO that could effectively improve PMTCT programmes. Despite this, prophylaxis coverage was still below 50% while coverage for HIV testing was less than 30% in pregnant women from the sub-Saharan Africa [4]. Average effectiveness of ARVs used at the time in preventing MTCT, largely nevirapine-based regimens, was 50% in Africa [13]. The most widely used prophylactic regimen before 2010 in the continent was short-course AZT plus NVP during labour [14]. Despite these being very simple regimens, prophylaxis coverage in most remote-settings in Africa was still very low by 2010 with some countries only covering 50% of exposed infants with the simple nevirapine-based regimen [15]. Option A (Table 2.1.1) was then adopted in many parts of Africa since 2010 and it had a notable impact on lowering HIV incidence rate in children by 2012 [16].

### 2.2.1 *Challenges in PMTCT programs in sub-Saharan Africa*

Despite widespread attempts to reduce MTCT globally, most low-to-middle income countries in sub-Saharan Africa have been slow in achieving the anticipated outcomes [16]. A number of factors are responsible. A major contributor has been the delay in making HIV testing routine for all pregnant women and it still is not in some settings [17]. Between 2007 and 2008 in Ivory Coast for example, only 60% of pregnant women were offered the opportunity to test for HIV of which 13% declined [18]. More problematic is poor coverage coupled with failure to adhere to treatment and ingestion of treatment is often not monitored, the focus being on the dispensing of drugs [19]. Coverage and adherence of the simplest regimen, single dose NVP, at the onset of labour in some settings has been shown to be poor and as low as 24% [18]. Retention of HIV positive women in pre-ART follow-up for appropriate timing of initiation of treatment has been shown to be a challenge [20–22]. A number of challenges also emanate from the health services perspective, and these include shortages of trained staff, incompetent administration, inadequate budgets and treatment stocks in clinics delaying initiation of therapy even to those who are loyal to the health services, [23–25][26]. Even though many of the countries in the region have achieved improved coverage after 2010, most of these problems remain a challenge in remote and rural settings [3].

## 2.3 PMTCT guidelines and implementation in South Africa

Plans for a uniform approach for treating pediatric HIV in South Africa began in earnest within one province around year 2000 and led to the first strategy being published and implemented in 2004 [27]. In 1999, the Western Cape province, through the Provincial Government, had the first PMTCT program at two clinics prior to any national policy on the issue of HIV treatment [28,29]. The results from a local clinic in the province proved the feasibility of implementing large-scale PMTCT services within routine urban clinic settings , the regimen comprising short-course AZT before delivery and NVP during labour and showing a MTCT rate of around 8-9% under a 22-26% exposure rate between 1999 and 2003 [30]. This regimen was adopted in many health centers across the country until Option A was introduced in 2008 when the National Department of Health was expanding treatment rollout in an attempt to make it available to all who needed it (Table 2.3) [31].

**Table 2.3:** The South African treatment and prophylaxis regimens implemented to prevent vertical transmission of HIV during pregnancy and delivery.

| **Year** | **Treatment (CD4 count ≤ 350cells/mm$^3$)** | **Prophylaxis (CD4 count >350cells/mm$^3$)** |
|---|---|---|
| 2001-2007[#] | sd-NVP: at onset of labour | sd-NVP: at onset of labour |
| 2008-2010 | HAART: daily, life-long from diagnosis | AZT: trimester 2<br>sd-NVP: at onset of labour |
| 2010-2013 | HAART: daily, life-long from diagnosis | sd-NVP & AZT(12 hourly): at onset of labour |

Treatment and prophylaxis options adapted from South Africa reports 2010 [31,32]. [#]The CD4 cutoff given applies if woman has clinical disease stage 3 otherwise eligible if CD4 count ≤ 200 cells/mm$^3$ or clinical disease is at stage 4[7].

### 2.3.1 *HIV maternal prevalence and MTCT rate in South Africa since 2006*

The infant-exposure rate in South Africa reached a plateau in the past 4+ years with a national average around 30% [33]. The largest nation-wide MTCT survey was performed in 2010 and confirmed previous reports of wide differences between provinces, which causes concern and required a shift from focussing on the national average estimates alone [2,31]. The transmission rates are also variable across provinces. In 2010 for example, while the national MTCT rate was 3.5%, provincial rates ranged from 1.4% (in Northern Cape province) to 5.9% (in the Free State province) [31]. HIV testing and treatment/prophylaxis coverage were already above 96% and 80% in all provinces respectively yet provinces such as the Free State had the worst MTCT outcomes even though it did not have the highest local HIV exposure rate (31% compared to 44% in KwaZulu Natal, Figure 2.3.1) [31]. The case of the Free State province indicates an alarming problem around effective coverage. In Figure 2.3.1, we show the differences between provinces which had the highest and lowest MTCT rate or infant-exposure rate to illustrate that low maternal HIV prevalence does not necessarily guarantee reduced vertical transmission rates. The discrepancies between the rates of infant exposure and infection and the reported ARV coverage also suggest poor quality routine data reporting.

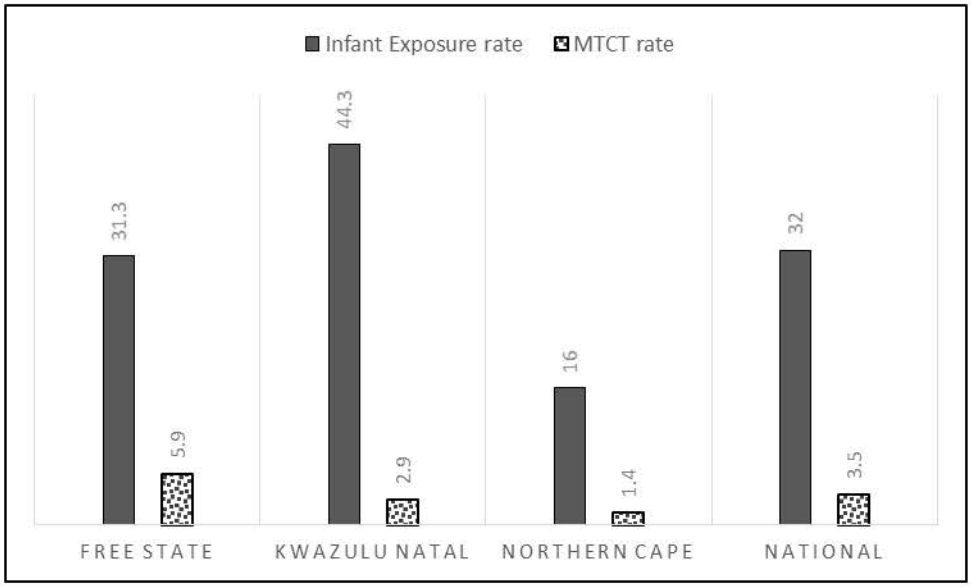


**Figure 2.3.1:** The 2010 HIV-infant exposure and vertical transmission rates in provinces with highest or lowest estimates and the national average [31]

Within-province differences also exist between antenatal service clusters. A good example is the Western Cape province which had the earliest local PMTCT interventions in the country, where sub-districts like Khayelitsha with long-standing antenatal services already achieved transmission rates below 3% by 2010 yet the provincial average was 3.9% [29,31,34]. District-level differences are observed throughout the country's provinces despite some having had received interventions at the same time [33].

### 2.3.2 *Challenges faced by South African PMTCT programs*

The challenges in South Africa faced around the PMTCT efforts are largely the same as the rest of sub-Saharan Africa. One most outstanding issue which has not been strongly taken into account is the socio-economic difference between provinces and districts which affects optimal usage of health care services. Some provinces, especially the Western Cape received successful interventions through well-structured antenatal clinics much earlier than other provinces [35] . Another common problem is about infected persons who have not reached critical clinical disease stages who generally do not visit health services ,thus making it difficult to keep track of their CD4 counts for accurately timing the initiating of therapy [18,33]. In pregnancy, testing coverage for HIV before delivery is high nationally. The 2010 routinely collected data reported a provincial coverage of at least 96% across the country but the challenge is in achieving early presentation, ideally during the first trimester, which impacts on vertical transmission [31,34,36,38]. Retention of those needing life-long therapy is also a challenge even in better resourced settings such as the well-established clinics in the Western Cape

Province [29,34]. Administrative discord, inadequate staffing and budget allocations in remote-setting is a major contributor to poor patient care and should be addressed urgently [25,37].

### 2.4 *Incompetent systems for collecting and reporting health data*

Health systems for accurately collecting and storing routine data in health facilities remain sub-optimal in many parts of sub-Saharan Africa including South Africa. Inconsistencies between data (HIV results or administered therapy) from clinic records and what is actually observed from cord-blood tests confirm lack of competence in data collection systems [39]. Inaccuracy arises from different levels of the system, beginning with the initial visit to a health facility at which not all patients are captured into the system [40,41]. Incomplete capturing of all data elements required leading to a large proportion of missing data which reduces sample sizes for accurate research analyses is also common [42]. Errors, such as typographical errors in patient personal identifiers and numerical figures, in recording data are also common and can mislead routine reporting and analyses [42]. Misdiagnosis of HIV leading to inappropriate treatment or delayed initiation of treatment is also an issue which needs to be dealt with urgently [43]. In many situations, incompetent and inadequately trained staff contribute to poor data collection and hence upgrading the data collection infrastructure will require simultaneous capacity building through staff training or employment of qualified and experienced personnel [41,44,45].

### 2.5 Conclusion: Eliminating the stagnant MTCT rates in South Africa

South Africa is one of the countries in the sub-Saharan region that has made impressive progress towards PMTCT service effectiveness, but the MTCT rate remains above 2.5% on average. This is mainly because of health service issues in remote and poor settings where even recorded routine data are still inaccurate and unreliable [39]. Lessons need to be taken from such areas in the country by closely monitoring and assessing the implementation, delivery and uptake of PMTCT programs at district and facility levels. Systems strengthening approaches, shown to improve health program outcomes, are what the country needs to adopt at present so as to effectively address context-specific needs [46].

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# 3. CHAPTER 3: Manuscript (for PLoS ONE Journal)

**Factors associated with Nevirapine adherence in the prevention of mother-to-child transmission of HIV in the Free State province, South Africa and discrepancies between service records and cord blood surveillance**

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**ABSTRACT** ***(266 words)***

Single-dose nevirapine coverage and uptake in rural settings is an important indicator of the feasibility of implementing the more complex triple therapy regimens in routine prevention of mother-to-child HIV transmission services.

A total of 1572 mother-infant pairs were included in a cross-sectional survey carried out in rural antenatal and delivery services from two districts in the Free State Province between 2007 and 2008. HIV testing and nevirapine prophylaxis data were collected by nurses and compared to anonymously linked cord-blood tests which confirmed HIV status and ingestion of nevirapine. Logistic regression was used to assess variables from the clinic surveillance data: age, gravidity, mode of delivery, timing of HIV testing and number of antenatal visits during pregnancy, as predictors of adherence to nevirapine.

Based on the Kappa statistic, clinic records under-estimated maternal HIV prevalence, 22% (95% CI 20-25) compared to 31% (95% CI 28-33) in cord-blood. In addition, cord-blood surveillance revealed that 19.6% of HIV-positive women given nevirapine according to the clinical records, did not ingest it (Kappa p-value<0.0001). Women who attended at least 4 antenatal visits were 4.7 times (95% CI 1.3-17.3, p-value=0.02) more likely to adhere than women who attended services once.

Uptake of all recommended antenatal cascade steps during pregnancy is important in improving adherence to a simple regimen such as single dose nevirapine. Repeat testing of HIV until delivery is important to ensure optimal prophylaxis coverage. Interventions both at the service provider and user levels are required to ensure that data are accurately collected and to prevent and manage seroconversion during pregnancy as well as optimize the effectiveness of the new Option-B guidelines in resource-limited settings.

**INTRODUCTION**

Nearly 50% of under-5 child deaths in South Africa are due to HIV infection through vertical transmission [1]. Although HIV incidence has declined among adults, HIV prevalence amongst pregnant women has stabilized at 30% due to a decrease in mortality as a result of the widespread roll out of ART. There is therefore an imperative to focus on improving the effectiveness of services and programmes designed for the prevention of mother-to-child transmissions (PMTCT). The need to balance feasibility of implementation of PMTCT programs, affordability and accessibility of treatment to all, has seen the South African government following the World Health Organization (WHO) PMTCT guidelines using cheaper drug options. The widely used regimen in the most recent years is Option A (life-long triple therapy if CD4 count <350cells/$mm^3$, otherwise dual prophylaxis starting with AZT and including single dose nevirapine (sd-NVP) at the onset of labour) [2]. Vertical transmission decreased from at least 9% a decade ago to 3.5% in 2010 [2]. However, the complicated Option A regimen does not simplify implementation and could contribute to delayed complete elimination of mother-to-child transmission (MTCT). The shift between one form of treatment to another during pregnancy, delivery and breastfeeding, often in the context of a range of different service delivery complexities, makes it challenging to ensure optimal service delivery [3]. Although the most recently recommended PMTCT regimen options, Option B (triple therapy for all pregnant women and cessation of treatment at 6 weeks post-delivery or one week after cessation of breast feeding) and Option B+ (life-long triple therapy for all HIV positive women - continued beyond child birth for life) [3], have not yet been widely adopted, the country has still made good progress, largely attributed to the earlier nevirapine-based regimens and Option A.

Despite this progress towards eliminating MTCT in South Africa, exposure and transmission rates vary widely. In 2010, MTCT rates ranged from 1.4% in the Northern Cape Province to 5.9% in the Free State province with exposure ranging between 16% (Northern Cape) and 44% (KwaZulu-Natal). The MTCT rate in the Free State province was the highest, and higher than the national average (3.5%) while the exposure rate (i.e., exposure to HIV positive mothers) was the same as the national average (30%) [2]. These outcomes reveal missed opportunities within the PMTCT programs in the Free State province. In addition, the roll-out of ARVs in the Free State failed to meet the demand. In 2007, coverage for all people living with HIV was only 25% despite roll-out across all districts in the province [4]. This was largely because the need was underestimated, resulting in patients waiting up-to 3 months to receive treatment, insufficient budget allocations, shortages of trained staff, poor administration, and the widely used vertical delivery approach which did not integrate ART programs into the routine public health facility systems and limited access [4–8]. Other factors that have contributed to the slow improvements in PMTCT outcomes in the country include young child-bearing age, poor uptake of the antenatal services during pregnancy, delayed HIV testing, social stigma and low staff-to-patient ratio [7,9–11].

Currently there is a need to closely assess individual antenatal services, particularly the health systems infrastructure and operations, and identify inter-provincial and inter-district differences in order to adopt more context-specific services. Although the most recent Option B and -B+ guidelines have been shown to achieve better MTCT outcomes and simpler than Option A, they are not likely to be effective if the provider and the user do not perform optimally [3,12]. Issues around adherence, follow-up, psycho-socio factors, trained and dedicated frontline service providers, adequate budgets and treatment supplies as well as competent data collection systems for monitoring and reporting coverage, need to be addressed urgently. Inefficient health system structures and poor data management not only prohibit good outcomes from even the simplest regimens but also report inaccurate results which can mislead future health policies [13].

In this study we assessed data from two resource-limited districts in the Free State Province. We report on PMTCT coverage at district level, i.e., HIV testing and dispensing of prophylaxis to pregnant women before delivery. The data were from 2007 to 2008 just before the

adoption of Option A, when sd-NVP was the regimen used for PMTCT. Discrepancies were identified between data routinely recorded by service providers at the antenatal clinics such as HIV test results and recorded nevirapine coverage and data from cord blood samples which confirm HIV status and ingestion of nevirapine. We also explore factors associated with coverage. Challenges learned from a simpler sd-NVP regimen give a good reflection on the state of the health systems and service delivery and hence the preparedness for implementation of future regimens.

## METHODS

### *Data*

A cross-sectional survey of clinic records and cord-blood surveillance data from the Free State Province of South Africa was performed. The data were collected as part of the PMTCT Effectiveness in Africa: Research and Linkages to care (PEARL) Study which set out to assess the effectiveness of PMTCT programs in four African countries (1), which received ethics approval from the University of Cape Town Research Ethics Committee. Briefly, in the PEARL study, posters and direct communication by clinic staff were used to inform women about the study and formal consent was waived, in order to limit performance bias related to the aims of the study, in particular the adherence to prophylaxis. Data were anonymously collected from clinic folders into clinic surveillance forms and assigned new study numbers in order to protect the privacy and confidentiality of the participants. Therefore the data were unlinked such that individual participants could not be traced from the information given in the clinic surveillance form. Cord-blood was drawn after delivery from the discarded placenta and analyses of these unlinked data were done in external laboratories from the clinics.

Table 1 presents variables which were available on the clinic surveillance form. The available PMTCT cascade information made it possible to assess HIV testing during pregnancy, maternal HIV prevalence and dispensing of prophylactic regimens. Cordblood tests were performed to confirm HIV status and adherence to nevirapine. Adherence to nevirapine is defined as the proportion of those who accepted NVP at the clinics and in addition to being

confirmed HIV-positive by cord-blood survey after delivery, had an HIV-positive cord-blood NVP test outcome (ingested NVP).

### *Statistical analyses and software*

Descriptive analyses were performed using non-parametric methods wherever the data failed to resemble a Gaussian distribution. Logistic regression was performed to identify factors influencing adherence to nevirapine which was treated as a binary variable (nevirapine present Yes/No). Associations and potential interactions between variables were assessed prior to implementing the logistic regression model. Only the independent variables which showed significant crude associations with adherence to nevirapine were added to the multivariate model. Potential confounding by other associated factors was taken into account when building the multivariate model, using forward stepwise regression.Analyses were performed in STATA software version SE 12.0 (STATCorp, Texas).

## RESULTS

The crude data, collected between 2007 and 2008, comprised 1679 records from women delivering infants in one of the 10 clinics servicing antenatal healthcare in the Motheo and Thabo Mofutsanyane districts of the Free State Province. The two districts were randomly selected from the total of five in the province and then clinics with the largest number of attendees within these districts were chosen. Of the 1679 women who delivered at the clinics, a total of 107 did not receive antenatal care before delivery and were excluded from the analyses. Therefore this study focussed on the 1572 women who attended ANC at least once during pregnancy and they all delivered at the same facility which provided them with antenatal care. There were no significant differences between any measurable variables between the two districts (Table 1).

The median age was 24 years, (Interquartile range (IQR):20-29 years). Most of the women had 1-2 children ever born to them (~70%), about 17% had 3 children while the rest had at least 4. A strong positive relationship existed between age and gravidity (chi-squared p-value<0.0001). Older women tended to have more children ever born to them and younger women (97% of the under 20 year old group) having their first or second pregnancy.

Primigravid women attended antenatal care (ANC) significantly more frequently than women having at least their third pregnancy (chi-squared p-value=0.002). Although the majority of women (90%) had normal vaginal delivery overall, a comparison between the different age-groups indicated that young women (12-19 years old) had the highest vaginal delivery proportion whilst the oldest women (31 years and older) had the highest proportion of caesarean deliveries (p-value<0.0001). Caesarean deliveries also appeared to be associated with more frequent antenatal visits (p-value<0.0001). A total of 1165 women tested for HIV according to the clinic surveillance records (Table 1). Of these, 10% (119) had been tested before the current pregnancy and 13.4% of them reported their past results as HIV-positive. Testing before the current pregnancy was not associated with having been pregnant before.

***PMTCT clinic coverage at district level according to routine data***

PMTCT coverage with respect to HIV testing at the clinics was 74% (1165) among the 1572 women who attended ANC. Routine data reported that HIV prevalence among women testing was 22.4% (261/1165). Of the 261 women who had a positive HIV test at the clinics, all of them were offered prophylaxis with 90% receiving single-dose nevirapine. The remaining 10% were already on HAART, AZT alone or a combination of AZT+NVP (Figure 1).

***HIV prevalence and adherence to nevirapine and discrepancies between clinic records and cord-blood surveillance***

A total of 1545 of the 1572 women were included in the cord-blood surveillance. The remainder (1.7%) were not tested because of either severe haemolysis during delivery, cord blood clotting or unavailability of specimen for unstated reasons. A total of 460 (29.8%) were found to be HIV positive. Nevirapine was tested on 441 of these HIV positive cord-blood samples and was confirmed present in only 54.4% of them (Figure 1).

The Kappa statistic was used to assess agreement between clinic records and cord blood survey. There were 1146 women who had a recorded HIV test result from both the clinic record and cord blood. The agreement for HIV results between the routine data and cord-blood test was 90.14% with a significant kappa statistic of 0.75 (p<0.0001), indicating moderate to substantial agreement. Of the 261 women with HIV positive outcomes at the clinics, 3% (8/261) were negative by cord blood tests (also confirmed not having ingested

nevirapine) and 12% (105/885) of those assigned negative outcomes at the clinics had HIV-positive cord-blood outcomes. This latter group may include late sero-converters. Overall, the prevalence of HIV in this sample of 1146 women was 31% based on cord-blood while the clinic records underestimated the prevalence at 22%.

The clinic reported that all HIV-positive women not already on triple therapy were offered nevirapine. Cord blood was tested for the presence of nevirapine on all 218 cord-blood samples from such women but 20% of them had no trace of nevirapine indicating that it was not ingested and that adherence was 80% (Figure 1). The Kappa statistics showed an agreement of 79.8% between the nevirapine dispensation clinic records and the cord-blood tests which, however, could be a result of chance (kappa statistic k=0) due to the clinic records assumption that all eligible mothers (i.e., HIV positive) offered nevirapine accepted and ingested it and that the records indicate that all eligible mothers with matched cord-blood samples were offered nevirapine (100% coverage).

***Factors influencing adherence to Nevirapine***

Woman's age, gravidity, number of ANC visits, mode of delivery and timing of first HIV test during pregnancy were assessed as possible predictors of adherence to nevirapine. Data were available for 216 women and 80.6 % (174/216) were adherent to nevirapine according to cord-blood. Bivariate analyses are shown in Table 2. In multivariate analyses, the model with only the number of ANC visits gave the best fit to the data, having the lowest AIC of 213.79 (Table 3). Women who had at least four ANC visits were 4.7 times more likely to adhere to nevirapine compared to those who attended only once (p-value=0.02, 95% CI 1.26-17.25). The results for 2-3 visits also indicate a trend that the higher the number of ANC visits, the more likely it is for women to adhere to their single-dose nevirapine (p-value=0.04, OR=4.3, 95% CI 1.04-17.75).

**DISCUSSION**

This study showed that antenatal HIV prevalence between 2007 and 2008 was high in the Free State, with 1 in 3 pregnant women being HIV-positive. The uptake of HIV testing was not optimal, with at least 25% of women failing to test for HIV before child-birth. Cord blood surveillance showed that nevirapine coverage was low at 54.4%. Cord-blood testing is important to confirm true maternal HIV prevalence during intrapartum as well as actual coverage and ingestion of prophylaxis. There are a number of possible reasons for the low uptake of testing. This may have been due the opt-in approach to counselling and testing where consent was obtained prior to testing. In 2010, this model was changed nationally to routine HIV testing in pregnancy, which has subsequently seen higher coverage in antenatal services [14]. Psycho-social factors such as denial and stigma were common at the time and most likely to be the largest contributors to sub-optimal testing [11,15].

The clinics reported 3% false HIV-positive results. Although records indicated these were offered nevirapine, cord blood tests confirmed that prophylaxis was not ingested. There are two main implications of this result. If these were not data capturing errors, giving false HIV-positive results can cause unnecessary psychological trauma to the recipients. They were most likely recording errors, which raises concern about the quality and reliability of data from health facilities. The 12% of women who were HIV-negative at ANC visit but confirmed HIV-positive at delivery could include late seroconverters who also contributed to the poor overall prophylaxis coverage observed here and in previous studies [16]. Our findings highlight the need to perform further HIV tests closer to delivery, or upon presentation in labour, to ensure that prophylaxis coverage is complete. While testing women of unknown status, or negative women in successive antenatal visits, or at 32 weeks gestation is a current guideline, it is unclear whether this is being fully implemented.

Data collection at primary health care services in South Africa, like other African countries, is still a challenge and requires major focus as inaccurate estimation of coverage, for example an 8% under-estimation of HIV prevalence in this dataset, can mislead policy strategies [13,17]. Erroneous data has been reported in a number of local PMTCT evaluation studies

and data error includes false-positive HIV results, data inaccuracy and missing information mainly due to inadequately trained staff [18–20]. Standardized methods for measuring programme effectiveness are crucial as confidence in current reported data is discouraged by the poor quality data. Cord-blood tests are not practically feasible as part of daily testing mechanisms in normal routine settings. It is therefore important to adequately train staff on accurate data collection, reporting and monitoring skills to ensure that the effectiveness of the Option B regimen which is currently being introduced is not compromised.

According to the clinic surveillance records, coverage for nevirapine was complete at 100%, i.e., everyone who had an HIV-positive results and not already on ART was offered nevirapine. However, it is not possible to ascertain whether coverage was indeed 100% or there were data entry errors. Assuming that the data are largely correct, cord blood tests confirmed that up to 20% of HIV positive women who were offered nevirapine failed to adhere. One problem that may be challenging to solve is the expected self-administration of nevirapine during labour. Although a single dose in itself is easier, labour is not a comfortable time to ascertain adherence on everyone. Service staff may need to encourage intake and ensure directly observed administration. Privacy should also be ensured as past reports have pointed out that stigma and fear of disclosure were some of the reasons for non-adherence [21,22]. This is particularly notable in the context of Option B, where ART is self-administered. Hence directly observed therapy could be part of the routine procedures so as enhance optimal uptake as well as give accurate records of prophylaxis ingestion.

There was lack of strong evidence for an association between adherence to prophylaxis with woman's age, gravidity, mode of delivery and timing of first HIV test. Although a previous study reported an association between age and general uptake of antenatal services, we did not find a specific relationship to nevirapine intake [9]. Although, we found mode of delivery and gravidity to be associated with the number of ANC visits, the two factors did not independently determine adherence outcomes. Caesarean deliveries were not common but were associated with older age and more frequent antenatal visits likely indicating need-based antenatal visits rather than standard routine for this subset of women.

Lack of maternal HIV testing is also a major determinant of PMTCT outcomes, hence we assessed whether women who self-initiated HIV testing prior to being pregnant would have had better outcomes than those who did not [10]. Similar to a previous study carried out in Africa, we found that the more frequent pregnant women visited the clinics antenatally, the better was the adherence to prophylaxis [17]. Therefore trust in the antenatal services needs to be encouraged in order to enhance optimal uptake of the PMTCT cascade and improve intervention outcomes. Cellphone technology intervention is one method which can be used to motivate and educate mothers along the PMTCT cascade via SMSs [23]. Negative psycho-social perceptions around HIV can be addressed through educating communities and mothers while also offering home-based follow-up counselling support for pregnant women to improve uptake and adherence [24,25]. Targeted psycho-social support offered within the clinic facilities through lay health workers has also improved uptake of the health services [26,27]

There are several limitations to this study. Data entry errors cannot be completely ruled out in some of the cascade records from routine data capturing. For instance, the subset of women who were recorded as HIV-positive in the clinic surveillance records but contrary confirmed negative in cord blood are likely to be a result of errors in data capturing by service staff. The cord-blood tests only confirmed nevirapine ingestion but adherence to ART on the remaining 10% of the participants was not carried out. Furthermore, women may have presented late in delivery and ingested NVP too late for it to reflect in the cord- blood, hence possibly underestimating the coverage. However, NVP is known to cross the placenta rapidly [9].

It has to be noted that the results are not generalizable across the entire Free State province because these data relate to non-urban settings. Also the data are from 2007-2008 and the PMTCT regimen has since changed. However, lessons from uptake, adherence and service operations still remain valid and are generalizable across other resource-limited settings in the country. Further studies will still need to be carried out to assess service provision and uptake in the case of home-based births, which were not available in this dataset, but are common in many South African rural communities.

**CONCLUSIONS**

In conclusion, evidence from this study confirms the need for more frequent use of antenatal services, hence measures need to be put in place to attract pregnant women to have trust and loyalty to these services. Frequent visits will allow for time to educate mothers about the importance of PMTCT and hence improve adherence which from this study is an evident problem. In particular, women need messages from the health service that encourage early first-time visits during the first trimester. Current evidence reports that less than half of pregnant women have their first visits before 20 weeks of gestation yet most recent guidelines further require much earlier initiation of therapy to eliminate MTCT [28,29]. Hindrances to visiting the clinic more often, such as transport, unplanned pregnancies and fear of disclosure, employment commitments and ease of access to facility, need to be assessed with respect to each community and clinic settings. Although great improvements have taken place at the national level, the impact of lower-level differences should not be ignored if the complete elimination of MTCT is to be achieved. In the case of the more effective option B+ which is simpler than Options –A and –B but likely more demanding than sd-NVP, a context-specific approach (at district and facility level) still needs to be used to improve coverage, especially in resource-limited settings like the rural Free State Province, in order to achieve optimal delivery, uptake, adherence and effectiveness. If adherence was poor for a simple sd-NVP regimen, the reasons for that need to be identified and dealt with in order to avoid compromising the more effective new regimens. Given the scientific evidence supporting Option B+, resources and efforts need to target these guidelines, however, it I important to highlight the lessons learned from a simpler (less effective regimen), in order to optimise the new intervention. The health system structures should be tailored to meet the local demand and socio-economic setting. Operational structures should be made available and adequate. Adequate and trained staffing is necessary for all different sectors linked to the PMTCT cascade, with additional focus on data reporting in the context of programme monitoring and evaluation. The role of community health workers should also be expanded to cover community awareness programs, follow-up, counselling and motivation for adherence.

**ACKNOWLEDGEMENTS**

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**FIGURE LEGENDS**

**Figure 1: Summary of clinic records and cord-blood survey for mother-infant PMTCT data.**
The PMTCT cascade showing **s**ummary of women delivering at clinics (solid clear boxes), confirmation of clinic HIV result & NVP intake with cord blood tests (dashed clear boxes) and overall HIV prevalence & NVP intake from cord-blood tests (dashed grey boxes).
*****Possibility of late sero-conversion and not entirely an error in clinic tests/records
[#]those who actually ingested NVP i.e. level of adherence
[¥]1.7% not tested in cord blood because either baby born before arrival at clinic, cord broke, stillbirth or forgot to take sample

**TABLES**

**Table 1:** PMTCT Cascade variables available in the clinic surveillance data

| | **Motheo District** | **Thabo M District** | **P-value~** | **Total (IQR or %)** |
|---|---|---|---|---|
| All women with >=1 ANC visits | 860 | 712 | - | 1572 |
| Age in years[#1] | | | | |
| Median (IQ) | 24 (21;30) | 24 (20;29) | 0.0975 | 24 (20;29) |
| % Proportion (95% CI) | | | 0.296 | |
| < 20 | 24 (21-27) | 26 (23-30) | | 396 (25.2%) |
| 20 – 30 | 54 (50-57) | 55 (51-59) | | 852 (54.3%) |
| > 30 | 22 (19-25) | 19 (16-22) | | 322 (20.5%) |
| Antenatal care visits | | | | |
| Median (IQ) | 4 (3;6) | 4 (3;6) | | 4 (3;6) |
| % Proportion (95% CI) | | | 0.086 | |
| 0 – 1 | 5 (4-7) | 7 (6-9) | | 97 (6.2%) |
| 2 – 3 | 31 (28-35) | 28 (25-31) | | 470 (29.9%) |
| ≥ 4 | 63 (60-67) | 64 (61-68) | | 1005 (63.9%) |
| Gravidity[#2] | | | | |
| Median (IQ) | 2 (1;3) | 2 (1;3) | 0.08 | 2 (1;3) |
| % Proportion (95% CI) | | | | |
| < 3 | 69 (66-73) | 73 (70-77) | | 1119 (71.3%) |
| 3 | 17 (14-20) | 17 (14-19) | | 264 (16.8%) |
| ≥ 4 | 14 (11-16) | 10 (8-12) | | 187 (11.9%) |
| Method of delivery[#3] | | | | |
| % Proportion (95% CI) | | | 0.03 | |
| Vaginal | 88 (86-91) | 92 (90-94) | | 1410 (89.9%) |
| Ceasarian section | 12 (9-14) | 8 (6-10) | | 159 (10.1%) |
| | | | | |
| HIV tested before delivery | 76 (73-79) | 72 (69-75) | 0.09 | 1165(74.1%) |
| HIV positive in clinic records | 22 (19-25) | 23 (20-27) | 0.565 | 261 (22.4%) |
| Offered NVP before delivery | 89 (84-95) | 92 (87-97) | 0.556 | 236 (90.4%) |
| *Other prophylaxis | 11 (5-16) | 8 (3-13) | 0.556 | 25 (9.6%) |

Thabo M = Thabo Mofutsanyane; ~Bivariate comparisons using Mann-Whitney test, chi-squared test or Kruskal-Wallis test; [#1]Missing age information for 2 participants (1 from each district); [#2]Missing gravidity information for 2 participants from Matheo districts; [#3]Missing mode of delivery for 3 participants (1 in Motheo & 2 in Thabo M); *Already on AZT/HAART/dual therapy (AZT+NVP)

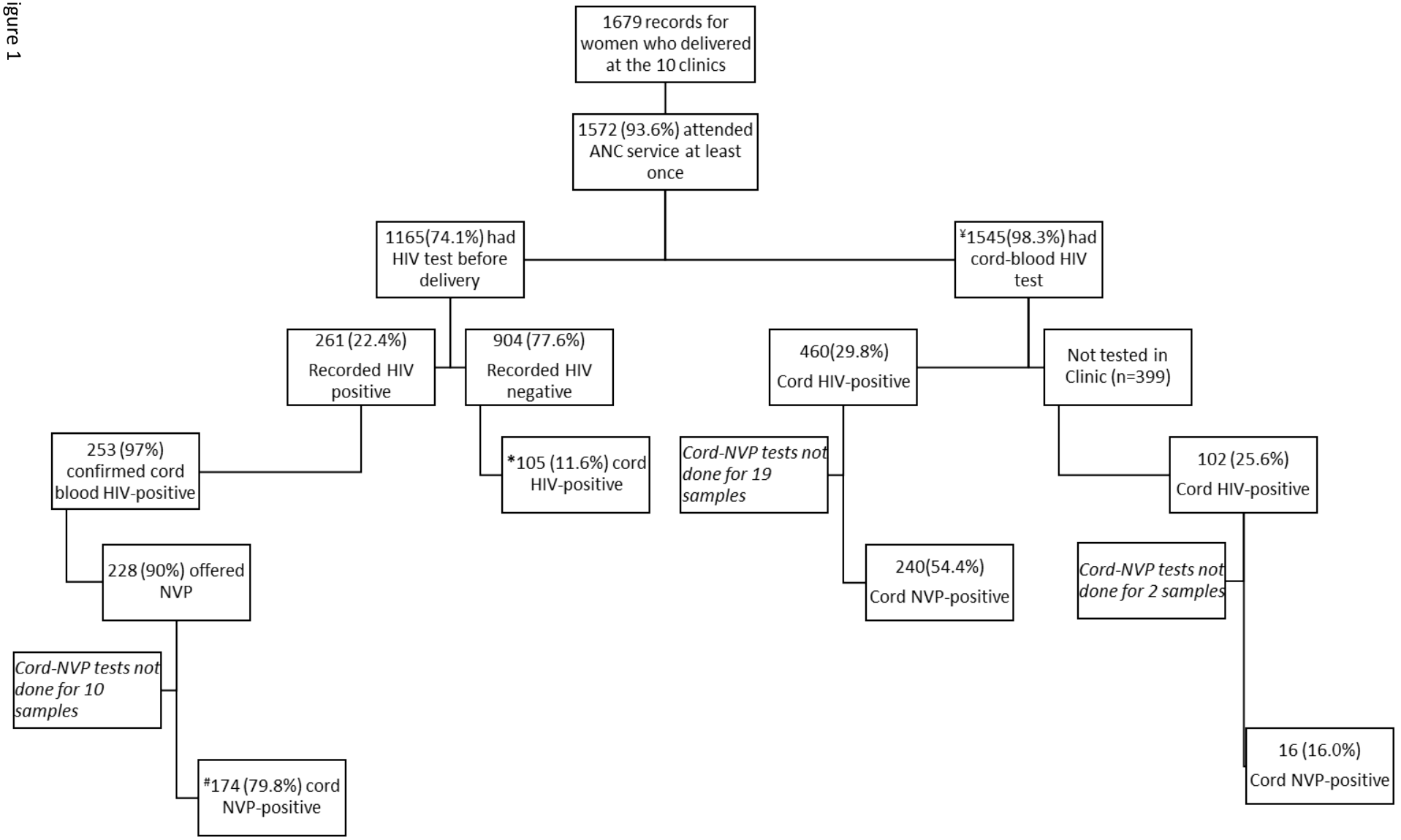
**Table 2:** Univariate analysis of predictors of adherence to nevirapine

| **Variables** | **Odds Ratio** | **P-value** |
|---|---|---|
| Age: >21 yrs compared to <=20 yrs old | 1.2 | 0.56 |
| Gravidity: >=3 compared to <3 | 1.0 | 0.96 |
| ANC visits: 2-3 compared to 1 visit | 4.3 | **0.04** |
| ANC visits: >=4 compared to 1 visit | 4.7 | **0.02** |
| Mode of delivery: caesarian compared to vaginal | 1.6 | 0.47 |
| HIV test timing: during pregnancy compared to before pregnancy | 0.3 | 0.26 |

**Table 3:** Details of the best-fitting model

| **Variable** | **Odds Ratio** | **P-values** | **95% CI** |
|---|---|---|---|
| ANC visits 2-3 vs 1 | 4.3 | 0.04 | 1.04 ; 17.75 |
| **ANC visits >=4 vs 1** | **4.7** | **0.02** | **1.26 ; 17.25** |
| Constant | 1.0 | 1.0 | 0.29 ; 3.45 |

Figure 1


1679 records for women who delivered at the 10 clinics
1572 (93.6%) attended ANC service at least once
1165(74.1%) had HIV test before delivery
¥1545(98.3%) had cord-blood HIV test
261 (22.4%) Recorded HIV positive
904 (77.6%) Recorded HIV negative
460(29.8%) Cord HIV-positive
Not tested in Clinic (n=399)
253 (97%) confirmed cord blood HIV-positive
*105 (11.6%) cord HIV-positive
Cord-NVP tests not done for 19 samples
102 (25.6%) Cord HIV-positive
228 (90%) offered NVP
240(54.4%) Cord NVP-positive
Cord-NVP tests not done for 2 samples
Cord-NVP tests not done for 10 samples
#174 (79.8%) cord NVP-positive
16 (16.0%) Cord NVP-positive

# APPENDIX A

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: preaward@curic.uct..ac.za

**09 February 2007**

**REC REF: 038/2007**

**Dr D Coetzee**
IIDMM
Public Health and Family Medicine
Falmouth Building, Level 1

Dear Dr Coetzee

**PROJECT TITLE: PMTCT EFFECTIVENESS IN AFRICA: RESEARCH AND LINKAGES TO CARE PART1: CORD BLOOD SURVEILLANCE PROTOCOL VERSION 1.0**

Thank you for submitting your study to the Research Ethics Committee for review.

I have pleasure in informing you that the Ethics Committee has **formally approved** the above mentioned study.
This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

**Please quote the REC. REF in all your correspondence.**

Yours sincerely

Osley Henley

pp **PROF.M BLOCKMAN**
**CHAIRPERSON, HSF HUMAN ETHICS**

lemjedi

# APPENDIX B

PE3 - SURVEILLANCE FORM  Study number ☐☐☐☐☐☐ (MONTH - YEAR)

**PART A** *Complete form with a blue or black pen*

1. Date of delivery ☐☐ - ☐☐ (MONTH - YEAR)
2. Mother's age (years) ☐☐
3. Gravidity* ☐ **Total number of pregnancies including this one and any past stillbirths/miscarriages/abortions*

4 Where did mother have her first prenatal visit? ◯No ANC visits ◯This facility ◯Other_____

5. Total number of ANC visits ☐☐

6. Date of last ANC visit: ☐☐ - ☐☐ (MONTH - YEAR)

7. HIV test before this pregnancy? ◯Yes, when? ☐☐ - ☐☐ (MONTH - YEAR) ◯No ◯Unknown

If No or Unknown Skip to question 9

8. Previous result? ◯Positive ◯Negative ◯Indeterminate ◯Not applicable

DURING THIS PREGNANCY:

9.Was mother pretest counseled for HIV? ◯Yes, when? ☐☐ - ☐☐ (MONTH - YEAR) ◯No ◯Unknown

10.Was HIV test performed? ◯Yes, when? ☐☐ - ☐☐ (MONTH - YEAR) ◯No ◯Unknown

11. If test performed, HIV test result: ◯Positive ◯Negative ◯Indeterminate ◯Unknown

12. Maternal NVP dispensed? ◯Yes ◯No ◯Unknown

13. AZT dispensed? ◯Yes, month started: ☐☐ - ☐☐ (MONTH - YEAR) ◯No ◯Unknown

14. HAART therapy dispensed? ◯Yes, month started: ☐☐ - ☐☐ (MONTH - YEAR) ◯No ◯Unknown

Staff name _____ Signature _____

**PART B**

15. Mode of delivery: ◯Vaginal ◯Caesarean

16. Hours after delivery the mother was discharged: ☐ 17.Hours after delivery the baby was discharged: ☐

18. Not yet discharged (tick in the box) ☐

19. Did the baby receive ARV prophylaxis? ◯No 20. Reason:

◯Mother was not tested ◯Baby died or was stillborn
◯Mother tested HIV-negative ◯Baby was transferred
◯Mother was transferred ◯Baby NVP given in ANC
◯Other_____

◯Yes 21. Number of hours after delivery: ☐

22. Which ARVs? ◯NVP only ◯AZT only ◯AZT + NVP
◯Other_____

23. Was mother discharged with replacement feeding? ◯Yes ◯No ◯Unknown

24. Birth weight of baby (in grams) ☐

25.In case of twins, birth weight of baby 2 (in grams) ☐

Staff name _____ Signature _____

PE3 - SURVEILLANCE FORM - v 2.0 23 OCT 07

# APPENDIX C

**PLoS ONE: Instruction to Authors** (http://www.plosone.org/static/guidelines )

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All manuscripts should be double-spaced and include line numbers and page numbers.

Manuscripts should begin with the ordered sections:

- Title
- Authors
- Affiliations
- Abstract
- Introduction

and end with the sections of:

- Acknowledgments
- References
- Figure Legends
- Tables

**Figures should not be included in the main manuscript file. Each figure must be prepared and submitted as an individual file.** Find more information about preparing figures here.

The title, authors, and affiliations should all be included on a title page as the first page of the manuscript file.

There are no explicit requirements for section organization between these beginning and ending sections. Articles may be organized in different ways and with different section titles, according to the authors' preference. In most cases, internal sections include:

- Materials and Methods
- Results
- Discussion
- Conclusions (optional)

*PLOS ONE* has no specific requirements for the order of these sections, and in some cases it may be appropriate to combine sections. Guidelines for individual sections can be found below.

Abbreviations should be kept to a minimum and defined upon first use in the text. Non-standard abbreviations should not be used unless they appear at least three times in the text.

Standardized nomenclature should be used as appropriate, including appropriate usage of species names and SI units.

**Guidelines for Standard Sections**

**Title**

Manuscripts must be submitted with both a full title and a short title, which will appear at the top of the PDF upon publication if accepted. Only the full title should be included in the manuscript file; the short title will be entered during the online submission process.

The full title must be 250 characters or fewer. It should be specific, descriptive, concise, and comprehensible to readers outside the subject field. Avoid abbreviations if possible. Where appropriate, authors should include the species or model system used (for biological papers) or type of study design (for clinical papers).

*Examples:*

- Impact of Cigarette Smoke Exposure on Innate Immunity: A *Caenorhabditis elegans* Model
- Solar Drinking Water Disinfection (SODIS) to Reduce Childhood Diarrhoea in Rural Bolivia: A Cluster-Randomized, Controlled Trial

The short title must be 50 characters or fewer and should state the topic of the paper.

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**Authors and Affiliations**

All author names should be listed in the following order:

- First names (or initials, if used),
- Middle names (or initials, if used), and
- Last names (surname, family name)

Each author should list an associated department, university, or organizational affiliation and its location, including city, state/province (if applicable), and country. If the article has been submitted on behalf of a consortium, all author names and affiliations should be listed at the end of the article.

**This information cannot be changed after initial submission, so please ensure that it is correct.**

To qualify for authorship, a researcher should contribute to **all** of the following:

1. Conception and design of the work, acquisition of data, or analysis and interpretation of data
2. Drafting the article or revising it critically for important intellectual content
3. Final approval of the version to be published

All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Those who contributed to the work but do not qualify for authorship should be listed in the acknowledgments.

When a large group or center has conducted the work, the author list should include the individuals whose contributions meet the criteria defined above, as well as the group name.

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**Abstract**
The abstract should:

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- Summarize the most important results and their significance
- Not exceed 300 words

Abstracts should **not** include:

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The introduction should:

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- Include a brief review of the key literature
- Note any relevant controversies or disagreements in the field
- Conclude with a brief statement of the overall aim of the work and a comment about whether that aim was achieved

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This section should provide enough detail to allow suitably skilled investigators to fully replicate your study. Specific information and/or protocols for new methods should be included in detail. If materials, methods, and protocols are well established, authors may cite articles where those protocols are described in detail, but the submission should include sufficient information to be understood independent of these references.

We encourage authors to submit detailed protocols for newer or less well-established methods as Supporting Information. Further information about formatting Supporting Information files, can be found here.

Methods sections of papers on research using **human or animal subjects and/or tissue or field sampling** must include required ethics statements. See the Reporting Guidelines for human research, clinical trials, animal research, and observational and field studies for more information.

Methods sections of papers with **data that should be deposited in a publicly available database** should specify where the data have been deposited and provide the relevant accession numbers and version numbers, if appropriate. Accession numbers should be provided in parentheses after the entity on first use. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication. A list of recommended repositories for different types of data can be found here.

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These sections may all be separate, or may be combined to create a mixed Results/Discussion section (commonly labeled "Results and Discussion") or a mixed Discussion/Conclusions section (commonly labeled "Discussion"). These sections may be further divided into subsections, each with a concise subheading, as appropriate. These sections have no word limit, but the language should be clear and concise.

Together, these sections should describe the results of the experiments, the interpretation of these results, and the conclusions that can be drawn. Authors should explain how the results relate to the hypothesis presented as the basis of the study and provide a succinct explanation of the implications of the findings, particularly in relation to previous related studies and potential future directions for research.

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People who contributed to the work but do not fit the *PLOS ONE* authorship criteria should be listed in the acknowledgments, along with their contributions. You must ensure that anyone named in the acknowledgments agrees to being so named.

Funding sources should **not** be included in the acknowledgments, or anywhere in the manuscript file. You will provide this information during the manuscript submission process.

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General guidelines

- Authors may cite any and all available works in the reference list.
- Authors may not cite unavailable and unpublished work, including manuscripts that have been submitted but not yet accepted (e.g., “unpublished work,” “data not shown”).
- If an article is submitted to a journal and also publicly available as a pre-print, the pre-print may be cited.
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Reference formatting

References must be listed at the end of the manuscript and numbered in the order that they appear in the text. In the text, citations should be indicated by the reference number in brackets. Journal name abbreviations should be those found in the NCBI databases. A number of reference software companies supply PLOS style files (e.g., Reference Manager, EndNote).

References should be formatted as follows:

- **Published papers**. Hou WR, Hou YL, Wu GF, Song Y, Su XL, et al. (2011) cDNA, genomic sequence cloning and overexpression of ribosomal protein gene L9 (rpL9) of the giant panda (*Ailuropoda melanoleuca*). Genet Mol Res 10: 1576-1588.
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- **Book chapters** Hansen B (1991) New York City epidemics and history for the public. In: Harden VA, Risse GB, editors. AIDS and the historian. Bethesda: National Institutes of Health. pp. 21-28.

- **Published media, not peer-reviewed. Examples: print or online newspapers and magazine articles.** Fountain H (29 Jan 2014). For Already Vulnerable Penguins, Study Finds Climate Change Is Another Danger. The New York Times. Available: http://www.nytimes.com/2014/01/30/science/earth/climate-change-taking-toll-on-penguins-study-finds.html. Accessed 17 March 2014.

- **New media, unregulated. Examples: blogs, websites, and other written works.** Allen L (01 Sept 2010) Announcing PLOS Blogs. Available: http://blogs.plos.org/plos/2010/09/announcing-plos-blogs/. Accessed 17 March 2014.

- **Master of Science and Doctor of Philosophy theses.** Wells A (1999) Exploring the development of the independent, electronic, scholarly journal. M.Sc. Thesis, The University of Sheffield. Available: http://cumincad.scix.net/cgi-bin/works/Show?2e09. Accessed 17 March 2014.

- **Databases and repositories. Examples: figshare, archive.com.** Roberts SB (2013) QPX Genome Browser Feature Tracks. Database: figshare. http://figshare.com/articles/QPX_Genome_Browser_Feature_Tracks/701214. Accessed 17 March 2014.

- **Multimedia. Examples: videos, movies, and TV shows.** Hitchcock A, producer and director (1954) Rear Window [Film]. Los Angeles: MGM.

**Tables**
Tables should be included at the end of the manuscript. All tables should have a concise title. Footnotes can be used to explain abbreviations. Citations should be indicated using the same style as outlined above. Tables occupying more than one printed page should be avoided, if possible. Larger tables can be published as Supporting Information. Please ensure that table formatting conforms to our Guidelines for table preparation (**or SEE 3 BELOW**)..

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Figures should **not** be included in the manuscript file, but figure legends should be. Guidelines for preparing figures can be found here (**or SEE 2 BELOW**).

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| **All figures** | Dimensions | Maximum: 17.35 cm W x 23.35 cm H<br>Minimum: 8.3 cm W |
| | Column fitting | Sized to fit columns in the final printed PDF |
| | Color mode | RGB (8 bit/channel) or grayscale only |
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| | Number/title/caption/image credit | Number/title/caption/image credit |
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| | File size | Under 10 MB |
| | Orientation | Vertical, not turned sideways |
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| | |
|---|---|
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